USE OF DIMETHYL SULFONE AS ISOTONICITY AGENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. 119 of Danish application no. PA 2002 01007 filed June 27, 2002 and U.S. application no. 60/394,154 filed July 3, 2002, the contents of each of which are fully incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates to a pharmaceutical composition for parenteral administration comprising a peptide and dimethyl sulfone and to the use of dimethyl sulfone as isotonicity agent in a pharmaceutical composition, especially a pharmaceutical composition comprising a peptide as the active ingredient.

BACKGROUND OF THE INVENTION

To avoid pain or tissue damage, pharmaceutical compositions for parenteral administration comprise an isotonicity agent to provide tonicity or osmolarity close to the body fluids at the administration site. Conventional isotonicity agents for parenteral peptide compositions are glycerol, dextrose, mannitol, lactose and salts such as sodium chloride.

The choice of isotonicity agent will affect the properties of the preparation as revealed by the chemical stability. For example aldehyde impurities of glycerol may result in transformation of the peptide thus resulting in a product with deteriorated stability.

Dimethyl sulfone is a well known organic compound which has been disclosed for different applications.

US 4,863,748 and 4,616,039 disclose dimethyl sulfone for use as a dietary supplement. US 4,973,605, US 4,559,329 and US 4,514,421 disclose dietary and pharmaceutical uses of dimethyl sulfone. US 4,568,547 discloses the use of dimethyl sulfone as a tabletting and granulating aid for pharmaceutically active agents. US 4,296,130 and US 4,477,469 disclose preparations containing dimethyl sulfone for softening skin and nails or for diluting blood. CA 1988-568512 discloses a formulation for treating cancer comprising dimethyl sulfone for enhancing or altering the penetration of the active agent to the tumour.

WO 01/26642 discloses a method for treating neurobehavioral disorders by administering a composition comprising amino acids, neurotransmitter precursors, vitamins, inhibitors of neurotransmitter degradation and/or immune function enhancers. Among the vitamins listed is dimethyl sulfone.

The present invention is based on the finding that dimethyl sulfone is useful as an isotonicity agent in pharmaceutical compositions for parenteral administration, especially pharmaceutical compositions for parenteral administration which comprise a peptide as the active ingredient.

DEFINITIONS

The following is a detailed definition of the terms used in the specification:

The term "peptide" as used herein is intended to include a compound formed by linking at least two amino acids through a peptide bond. The term comprises oligopeptides containing fewer than 10 amino acids as well as polypeptides containing at least 10 amino acids. The term includes naturally occurring peptides, including proteins, as well as synthetic peptides. The term is also intended to include modified peptides, eg alkylated, acylated peptides, etc.

The term "parenteral administration" as used herein means that the administration is not through the alimentary canal but rather through some other route, such as via the subcutaneous, intramuscular, intrathecal, pulmonal, intravenous, intradermal, intraspinal or intrasternal route. The term also covers ophthalmic administration and topical administration.

The term "analogue" as used herein designates a peptide wherein one or more amino acid residues of the parent peptide have been substituted by another amino acid residue and/or wherein one or more amino acid residues of the parent peptide have been deleted and/or wherein one or more amino acid residues have been added to the parent peptide. Such addition can take place either in the peptide, at the N-terminal end or at the C-terminal end of the parent peptide, or any combination thereof.

The term "derivative" as used herein designates a peptide in which one or more of the amino acid residues of the parent peptide or analogue of the parent peptide have been chemically modified, eg by alkylation, acylation, ester formation or amide formation.

DESCRIPTION OF THE INVENTION

The present invention relates to a pharmaceutical composition for parenteral administration, which comprises a peptide and dimethyl sulfone.

Dimethyl sulfone which is also designated methylsulfonylmethane or MSM may be prepared from dimethyl sulfoxide by oxidation. It can be obtained in highly purified form as crystals with a melting point at about 110 °C and has a well defined boiling point at 238 °C. It is commercially available at a low price. It is non-toxic and non-allergenic. Furthermore, it is very soluble in water. These properties make it very attractive for use in pharmaceutical compositions. Dimethyl sulfone is very stable and does not deteriorate the peptide in the

pharmaceutical composition. Accordingly, very stable pharmaceutical compositions are provided.

Dimethyl sulfone is used in an amount to make the pharmaceutical composition isotonic with the site of administration. The amount has to be adjusted based on the other ingredients of the pharmaceutical composition which may also contribute to isotonicity.

In one embodiment, the amount of dimethyl sulfone is of from 40 to 400 mM, such as of from 125 to 350 mM.

In another embodiment, the pharmaceutical composition is a solution.

In yet another embodiment, the pharmaceutical composition is a suspension.

The pharmaceutical composition is intended for parenteral administration. In one embodiment, the pharmaceutical composition is adapted for administration by injection or infusion, such as subcutaneous administration, intramuscular administration or intravenous administration.

In another embodiment, the pharmaceutical composition is adapted for pulmonal administration.

In yet her embodiment, the pharmaceutical composition is adapted for ophthalmic administration or topical administration.

The pharmaceutical composition comprises a peptide as active ingredient. In one embodiment, the peptide is human growth hormone, GLP-1, GLP-2, insulin, Factor VII, Factor VIII, erythropoeitin (EPO), glucagon, interleukin, such as interleukin-2 (IL-2), interferon-α or interferon-β, or an analogue thereof, or a derivative of any such peptide or analogue.

In another embodiment, the peptide is human insulin or an analogue thereof, or a derivative of human insulin or the human insulin analogue, such as human insulin, Asp(B28)-human insulin, Lys(B28) Pro(B29)-human insulin, Lys(B3) Glu(B29)-human insulin, $N^{\varepsilon B29}$-tetradecanoyl des (B30)-human insulin, Gly(A21) Arg(B31) Arg(B32)-human insulin or $N^{\varepsilon B29}$-litocholoyl-γ-glutamyl des (B30)-human insulin.

In yet another embodiment, the peptide is Gly(8)-human GLP-1, Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys(26)-human GLP-1(7-37)OH or Gly(2)-human GLP-2.

In a further aspect the invention relates to the use of dimethyl sulfone as an isotonicity agent in a pharmaceutical composition for parenteral administration.

In yet a further aspect, the invention relates to the use of dimethyl sulfone as an isotonicity agent in a pharmaceutical composition for parenteral administration comprising a peptide as the active ingredient.

In one embodiment, the amount of dimethyl sulfone in the pharmaceutical composition is of from 40 to 400 mM, such as of from 125 to 350 mM.

In another embodiment, the pharmaceutical composition is a solution.

In yet another embodiment, the pharmaceutical composition is a suspension.

In still another embodiment, the pharmaceutical composition is adapted for administration by injection or infusion, such as subcutaneous administration, intramuscular administration or intravenous administration.

In a further embodiment, the pharmaceutical composition is adapted for pulmonal administration.

In a further embodiment, the pharmaceutical composition is adapted for ophthalmic administration or topical administration.

In yet a further embodiment, the peptide is human growth hormone, GLP-1, GLP-2, insulin, Factor VII, Factor VIII, erythropoeitin (EPO), glucagon, interleukin, such as interleukin-2 (IL-2), interferon-α or interferon-β, or an analogue thereof, or a derivative of any such peptide or analogue.

In still a further embodiment, the peptide is human insulin or an analogue thereof, or a derivative of human insulin or the human insulin analogue, such as human insulin, Asp(B28)-human insulin, Lys(B28) Pro(B29)-human insulin, Lys(B3) Glu(B29)-human insulin, $N^{\varepsilon B29}$-tetradecanoyl des (B30)-human insulin, Gly(A21) Arg(B31) Arg(B32)-human insulin or $N^{\varepsilon B29}$–litocholoyl-γ-glutamyl des (B30)-human insulin.

In another embodiment, the peptide is Gly(8)-human GLP-1, Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys(26)-human GLP-1(7-37)OH or Gly(2)-human GLP-2.

PHARMACEUTICAL COMPOSITIONS

The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions according to the invention are intended for parenteral administration, such as subcutaneous, intramuscular, intrathecal, intravenous, intradermal, intraspinal or intrasternal administration. Other suitable administration routes are ophthalmic administration or topical administration for treating open wounds, ulcers, bedsores, pressure sores and burns.

It will be appreciated that the preferred route of administration will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Suitable administration forms include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include ophthalmic preparations such as eye drops and eye ointments and topical preparations such as wound dressings.

EXAMPLES

Example 1

Formulation of dissolved human insulin preparation containing dimethyl sulfone

74.9 mg of Zn-crystallized human insulin is dispersed in 2 ml of water and dissolved by addition of 32.5 µl of 2N hydrochloric acid. Then the following ingredients are added:

2.0 ml of 160 mM m-cresol solution
2.0 ml of 160 mM phenol solution
376 mg of dimethyl sulfone
1.0 ml of 140 mM disodium hydrogen phosphate solution
1.0 ml of 200 mM sodium chloride solution
10 ml of water

The pH is adjusted to 7.3 with diluted hydrochloric acid or sodium hydroxide and water is added to a total volume of 20.0 ml. The resulting solution is finally sterilized by filtration.

Example 2

Comparison of the chemical stability of 3 formulations of dissolved human insulin

Formulation I is prepared according to example 1.

Formulation II is prepared according to example 1 with the exception that the dimethyl sulfone is omitted.

Formulation III is prepared according to example 1 with the exception that the dimethyl sulfone is replaced by 368 mg of glycerol.

The formulations were stored in closed 1 ml HPLC vials at 4 °C and at 25 °C, respectively. After storage for 10 weeks the formulations were analyzed by reverse phase HPLC on a 4.6 mm X 150 mm Waters SymmetryShield RP_8 (3.5 µm) column eluted at 30 °C

by a buffer system A (0.2 M sodium sulphate, 0.04 M sodium phosphate, pH 7.2 in 10% (v/v) acetonitrile) with 19% B (70% (v/v) acetonitrile) for 21 min, then with 24% B for 30 min and finally with a linear gradient from 24% B to 39% B over 30 min.

The AUC for the side peaks in percentage of the total AUC for the insulin-related peaks was calculated as a measure of purity. Thus, a low number indicates a high degree of purity. The difference in purity between the human insulin solutions stored at 4 °C and 25 °C, respectively, is shown in the table for each of the formulations.

Formulation	Δ% Purity
I (dimethyl sulfone)	1.64
II (no isotonicity agent)	**1.62**
III (glycerol)	1.92

The results show that the content of dimethyl sulfone does not impair the chemical stability of the insulin in the formulation and that the insulin is substantially less stable when dimethyl sulfone is replaced by glycerol in the formulation.

Example 3

Formulation of NPH-crystallized human insulin preparation containing dimethyl sulfone

Solution A:

74.5 mg of Zn-crystallized human insulin is dispersed in 2 ml of water and dissolved by addition of 34 µl of 2N hydrochloric acid. Then the following ingredients are added:

650 µl of 160 mM m-cresol solution

430 µl of 160 mM phenol solution

176 mg of dimethyl sulfone

35.8 µl of zinc chloride solution (10 mg Zn/ml)

750 µl of protamine sulphate solution (10 mg/ml)

Water is added to a total volume of 10 ml.

Solution B:

The following ingredients are mixed:

2.0 ml of 140 mM disodium hydrogen phosphate

650 µl of 160 mM m-cresol

430 µl of 160 mM phenol

176 mg of dimethyl sulfone
8 µl of 2N sodium hydroxide

Water is added to a total volume of 10 ml. Solution A and solution B are sterilized by filtration and then mixed. The resulting suspension is left at 23°C and after overnight standing the crystallization is complete.

Example 4

Formulation of a preparation of dissolved Asp(B28)-human insulin analogue containing dimethyl sulfone

151.9 mg of Zn-free Asp(B28)-human insulin (can be prepared as described in eg EP 214 826) is dispersed in 2 ml of water and dissolved by addition of 65 µl of 2N hydrochloric acid. Then the following excipients are added with gentle stirring:

78.4 µl of zinc chloride solution (10 mg Zn/ml)
4.0 ml of 160 mM m-cresol solution
4.0 ml of 160 mM phenol solution
752 mg of dimethyl sulfone
50 mg of disodium hydrogen phosphate, dihydrate
23.5 mg of sodium chloride
25 ml of water

The pH is adjusted to 7.3 with diluted hydrochloric acid or sodium hydroxide and water is added to a total volume of 40.0 ml. The resulting solution is finally sterilized by filtration.

Example 5

Formulation of a dissolved preparation of Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys(26)-human GLP-1(7-37)OH containing dimethyl sulfone

The following ingredients are mixed:

3.2 ml of 50 mM disodium hydrogen phosphate solution
10.6 ml of 100 mM phenol solution
382 mg of dimethyl sulfone
5 ml of water

The pH is adjusted to 7.4 with diluted hydrochloric acid and water is added to a total volume of 20 ml.

40 mg of Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys(26)-human GLP-1(7-37)OH (can be prepared as described in eg WO 98/08871) is added and dissolved by gentle stirring. The resulting solution is sterilized by filtration, if necessary, after readjustment of the pH to 7.4.

Example 6

Formulation of a dissolved preparation of human growth hormone containing dimethyl sulfone

The following ingredients are mixed:

6.8 mg of L-histidine

30 mg of poloxamer 188

207 mg of dimethyl sulfone

3.2 ml of 100 mM phenol solution

5 ml of water

The pH is adjusted to 6.2 with diluted hydrochloric acid and water is added to a total volume of 10 ml.

67 mg of human growth hormone (can be prepared as described in eg EP 217 814 or EP 218 651) is added and dissolved by gentle stirring. The resulting solution is sterilized by filtration, if necessary, after readjustment of the pH to 6.2.

Example 7

Formulation of a freeze-dried preparation of human FVIIa containing dimethyl sulphon

The following ingredients are mixed:

FVIIa	0.6 mg/ml
$CaCl_2$	10 mM
Glycylglycine	10 mM
Dimethyl sulphone	8.3 mg/ml
Tween 80	0.07 mg/ml
Mannitol	30 mg/ml

pH 5.5

The pH is adjusted to 5.5 with NaOH/HCl. The solution is sterilized by filtration and filled into sterile glass vials. The vials are freeze-dried, closed with rubber stoppers and